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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,649	02/27/2004	Thomas D. Madden	480208.408D1	7233

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/788,649	MADDEN ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-13,17 and 22-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-13,17 and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-11-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 10-11-05 is acknowledged.

Claims included in the prosecution are 7-13, 17 and 22-29.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 7-13 and17-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sarris (6,723,338) in combination with either Young or WO 91/04019, OR Young or WO in view of Sarris.

Sarris discloses a method of treatment of lymphoma by administering liposome-encapsulated vinca alkaloids such as vincristine and vinorelbine and camptothecins (Topotecan). Among the methods of administration taught are subcutaneous and intramuscular routes (abstract, col. 7, line 64 through col. 8, line 8, col. 14, lines 45-48). What is lacking in Sarris is the inclusion of empty liposomes in the compositions.

Young discloses liposomes containing an active agent entrapped within and empty liposomes. The ratio of liposomes containing the active agent to empty liposomes is 0.1-1 to 10-200. The active agents taught by Young are anti-tumor agents

such as doxorubicin. According to Young, the administration of such a mixture selectively controls the rate of release of the liposome entrapped active agent from an intramuscular or subcutaneous injection site (abstract, col. 4, line 40 through col. 6, line 23, col. 10, lines 35-49, col. 15, lines 10-34, Example VIII and claims).

WO as pointed out before, discloses liposomes containing an active agent entrapped within and empty liposomes. The ratio of liposomes containing the active agent to the empty liposomes is 1:1 to 1:10,000. The active agents taught by WO include interferons and chemotactic peptides. The liposomal lipids taught include sphingomyelin and cholesterol. The ratios of the active agent to lipid fall within the claimed amounts. According to WO, the addition of empty liposomes increases the bioavailability of the therapeutic agent (abstract, page 6, line 17 through page 7, line 33, page 8, line 4 through page 9, line 17 and claims, in particular, claims 8, 21, 22, 27, 31 and 33).

It would have been obvious to one of ordinary skill in the art to include empty liposomes in the compositions of Sarris since according to Young, and WO the empty liposomes influence the release of the active agent.

Alternately, to use vinca alkaloids as the active agents in the compositions of Young, or WO would have been obvious to one of ordinary skill in the art if the cancer to be treated were a lymphoma and as taught by Sarris, liposome encapsulated vinca alkaloids are effective in the treatment of lymphoma.

3. Claims 7-13, 17, 22 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491) of record in combination with either Young or WO 91/04019 cited above.

Kirpotin discloses liposomal compositions wherein the active agent is in the precipitated form. The active agent according to Kirpotin can be any compound with ionizable groups. The active agents suggested by Kirpotin are antineoplastic agents, doxorubicin, vincristin, vinblastine and others. The liposomes are made of various phospholipids including sphingomyelin; the liposomes contain cholesterol. The lipid drug ratios in Kirpotin also appear to fall within the claimed ratios (abstract; col. 4, line 54 through col. 6, line 18; col. 9, lines 22-67; examples and claims). What are lacking in Kirpotin are the teachings of the inclusion of empty liposomes.

Young as pointed out above, discloses liposomes containing an active agent entrapped within and empty liposomes. The ratios of liposomes containing the active agent to empty liposomes are 0.1-1 to 10-200. The active agents taught by Young are anti-tumor agents such as doxorubicin. According to Young, the administration of such a mixture selectively controls the rate of release of the liposome entrapped active agent (abstract, col. 4, line 40 through col. 6, line 23, col. 10, lines 35-49, col. 15, lines 10-34, Example VIII and claims).

WO as pointed out before, discloses liposomes containing an active agent entrapped within and empty liposomes. The ratio of liposomes containing the active agent to the empty liposomes is 1:1 to 1:10,000. The active agents taught by WO

include interferons and chemotactic peptides. The liposomal lipids taught include sphingomyelin and cholesterol. The ratios of the active agent to lipid fall within the claimed amounts. According to WO, the addition of empty liposomes increases the bioavailability of the therapeutic agent (abstract, page 6, line 17 through page 7, line 33, page 8, line 4 through page 9, line 17 and claims, in particular, claims 8, 21, 22, 27, 31 and 33).

The inclusion of empty liposomes in the liposome compositions of Kirpotin would have been obvious to one of ordinary skill in the since such an inclusion would selectively controls the rate of release of the liposome entrapped active agent as taught by Young or empty liposomes increase the bioavailability of the therapeutic agent as taught by WO.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the teachings of WO 99 are limited to camptothecins which are known in the art to be administered intravenously and therefore the skilled artisan would have no motivation to modify the teachings of WO 99 by adding empty liposomes to the liposomal camptothecins of WO 99 on the basis of either Young or WO 91 since their teachings regarding empty liposomes is clearly limited to SC and IM administered liposomal drug formulations. This argument is not found to be persuasive since as pointed out before WO 99 does not disclose intravenous delivery as the ***only means of delivery.*** On page 15, lines 13-19 WO 99 teaches that the route of delivery of liposome can also affect their distribution in the body and various routes of administration are envisioned. These statements imply the inclusion of the SC and IM

administrations of Young or WO 91. Furthermore, the examiner points out that instant claims are drawn to composition claims and not to 'method of intravenous administration of the compounds and the surprising results as argued by applicant appear to pertain to the mode of delivery, i.e., intravenous injection.

4. Claims 7-13, 17, 22 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491) of record in combination with either Young or WO 91/04019 cited above, further in view of Sarris (6,723,338) cited above.

The teachings of Kirpotin, Young and WO 91 have been discussed above. What is lacking in Kirpotin is the suggestion as to the mode of administration of the liposomes encapsulating vinca alkaloids.

Sarris as pointed out above discloses a method of treatment of lymphoma by administering liposome-encapsulated vinca alkaloids such as vincristine and vinorelbine and camptothecins (Topotecan). Among the methods of administration taught are subcutaneous and intramuscular routes (abstract, col. 7, line 64 through col. 8, line 8, col. 14, lines 45-48).

One of ordinary skill in the art would be motivated to include the empty liposomes of Young or WO 91 in Kirpotin's compositions if the desired mode of administration is either subcutaneous or intramuscular, since Young, and WO both teach enhanced bioavailability and since Sarris teaches that vinca alkaloids may be administered by subcutaneous or intramuscular injection routes.

5. Claims 7-9, 17 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 of record in combination with either Young or WO 91/04019 cited above.

WO 99 discloses liposomal formulations containing various camptothecins in a precipitated form. According to WO, any phospholipid capable of forming liposomes can be used in preparing liposomes. The liposomes also contain cholesterol. The drug-lipid ratios taught by WO appear to fall within the claimed ratios (abstract, page 8, lines 8 through page 11, line 15; page 12, lines 1-7, Examples 3 and 4 and claims). What are lacking in WO are the teachings of the use of empty liposomes and the use of vinca alkaloids as the anti-tumor agents.

The teachings of Young and WO 91 have been discussed above.

The inclusion of empty liposomes in the liposome compositions of WO 99 would have been obvious to one of ordinary skill in the since such an inclusion would selectively controls the rate of release of the liposome entrapped active agent as taught by Young or empty liposomes increase the bioavailability of the therapeutic agent as taught by WO 91. The use of vinca alkaloids instead of camptothecins with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since both Young and WO 91 teach the applicability of the method to any active agent.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that Young fails to teach that the release rate of intravenously administered liposomal composition can be influenced by including

empty liposomes and that camptothecins and vinca alkaloids are known in the art to be administered intravenously. This argument is not found to be persuasive since the rejected claims are composition claims and not method of intravenously administering the composition.

5. Claims 7-9, 17 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 of record in combination with either Young or WO 91/04019 cited above, further in view of Sarris (6,723,338) or Giovanella (5,552,154).

The teachings of WO 99, Young and WO 91 have been discussed above.

Sarris as pointed out above discloses a method of treatment of lymphoma by administering liposome-encapsulated vinca alkaloids such as vincristine and vinorelbine and camptothecins (Topotecan). Among the methods of administration taught are subcutaneous and intramuscular routes (abstract, col. 7, line 64 through col. 8, line 8, col. 14, lines 45-48).

Giovanella discloses intramuscular administration of camptothecins (abstract, col. 5, lines 10-13).

One of ordinary skill in the art would be motivated to include the empty liposomes of Young or WO 91 in the compositions of WO 99, if the desired mode of administration is either subcutaneous or intramuscular, since Young, and WO both teach enhanced bioavailability and since the references of Sarris or Giovanella show that camptothecins may be administered by subcutaneous or intramuscular injection routes.

Applicant's arguments based on Dr. Goldie's declaration have been carefully reviewed, but are not persuasive. According to Dr. Goldie, Camptothecins and vinca

alkaloids are not approved by the Food and Drug Administration for subcutaneous or intramuscular administration, primarily due to cytotoxic effects associated with such local administration. It is Dr. Goldie's opinion that an oncologist would not administer camptothecins or vinca alkaloids subcutaneously or intramuscularly, whether in free form or encapsulated in liposomes, for the reasons described supra. Furthermore, it is my opinion that the references cited by the Examiner and the publications referred to herein do not provide motivation for an oncologist to administer camptothecins or vinca alkaloids subcutaneously or intramuscularly. FDA' approval or disapproval is for human administration and not for the administration to animals. As pointed out above, instant claims are composition claims and are not drawn to method of intravenous administration of the composition to humans. Irrespective of FDA's approval or disapproval, the prior art cited by the examiner shows clearly suggestive of the subcutaneous and intramuscular modes of administration of camptothecins and vinca alkaloids. The arguments thus, are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK